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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

18M1/0123

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ART UNIT	PAPER NUMBER
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 10/27/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 110-124 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☒ Claim(s) 119-122 is/are allowed.
☒ Claim(s) 110-118 & 123-124 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____.
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III DETAILED ACTION

1. Cancellation of Claims 106, 107, and 109 in Paper No. 31 filed 27 October 1997 is acknowledged. Claims 110-124 are pending and currently under examination.

Double Patenting

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 110-124 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 91-97 of U.S. Patent 5,656,272. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to methods of treating TNFα mediated disease using anti-TNFα antibodies. Applicants agreement to file a terminal disclaimer upon resolution of the remaining rejections is acknowledged.

Claim Rejections - 35 USC § 112

Claims 123 and 124 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some immune and inflammatory diseases, does not reasonably provide enablement for inflammatory diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claim.

The claims are drawn to a method of treating TNF-alpha mediated inflammatory diseases in a human comprising administering an anti-TNF chimeric antibody. Claim 124 is further drawn to the chimeric antibody cA2. The claimed invention is not enabled for the scope of the TNF-alpha mediated diseases encompassed by the claims based on the unpredictability in the art and lack of guidance provided by the specification. For example, the specification fails to enable one of skill in the art how to make and use an anti-TNF-alpha antibody for use in preventing and treating septic shock which is an inflammatory disease. The state of the art was, at the time the invention was made, and still is unpredictable with regards to making and using anti-TNF-alpha antibodies for use in treating septic shock. Natanson et al. (Annals of Internal Medicine, 1994) teach that TNF alpha binding proteins have not been shown to improve outcome in the treatment of human sepsis and septic shock and may, in

fact, be potentially harmful. Natanson et al. goes on to teach "Identification of patients in whom an exaggerated cytokine response develops and who are thus likely to benefit from anti-inflammatory treatment strategies remains an important issue. The timing, duration, and delivery of these therapies to tissue compartments (to the peritoneum or lung, for example) are other critical unresolved issues. Clearly, suppression of cytokine function may be injurious for some patients, and that effect of these agents on bacterial clearance, nosocomial infection, and the reparative processes after tissue damage from sepsis requires further investigation. Whether it is clinically feasible to inhibit cytokines and limit their harmful effects while preserving their ability to perform necessary beneficial functions is unknown. The lack of efficacy in four clinical trials and harm produced by one TNF antagonist prompts questions about the methodology used, the viability of this therapeutic approach, or both." See pp.774-777, p.776 column 2 in particular.

Therefore, it is clear that the art teaches that the results from animal models of septic shock cannot be extrapolated to humans. Furthermore, the specification does not teach identifying patients who would benefit from treatment and the timing, duration and delivery of the compositions to humans that would benefit the patient without producing harm. Therefore, in view of the lack of guidance in the specification and in view of

the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method of treating TNF-alpha mediated diseases using a composition comprising anti-TNF-alpha chimeric antibodies.

2. Claim 112 remains rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The antibody cA2 should be referred to by its accession number or sequence not to its laboratory name which may be shared by other antibodies in the art.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Although Applicants can be their own lexicographer, they must nevertheless particularly point out and distinctly claim the subject matter which applicant regards as the invention. The name cA2 has not definiteness. It is an arbitrary name that may also be used by other laboratories. If Applicant does not chose to identify the cA2 antibody by an accession number they may alternatively identify the cA2 antibody by either its amino acid or DNA sequence which would also be a unique identifier.

Claim Rejections - 35 USC § 103

3. Claims 110, 111, 113-118 and 123 remain rejected under 35 U.S.C. § 103 as being unpatentable over any one of either Aggarwal et al. (US Patent 5,672,347) or Shalaby et al. (Transplantation, 1989) or Brennan et al. (The Lancet, 1989) or Piguet et al. (J. Exp. Med., 1987) or Piguet et al. (J. Exp. Med., 1989) or Grau et al. (Science, 1987) each in view of Moller et al. (U.S. Patent No. 5,231,024 or Cytokine, 1990) or Rathjen et al. (WO 91/02078) each in combination with either Morrison et al. (Science, 1985, 225:1202-1207) or Morrison et al. (Hospital Practice 1989).

The claims are drawn to a method of treating TNFα mediated disease, other than those resulting from infection, in a human comprising administering an anti-TNF chimeric antibody. Claims are further drawn to chimeric antibodies that bind particular epitopes, constant regions with particular isotypes, antibodies that compete with A2, and have an isotype of IgG1.

Aggarwal et al. teach therapy of graft rejections, arthritis, and other autoimmune and inflammatory disorders using anti-TNF (see column 1 for example). Aggarwal et al. teach modes and doses of treatment (see column 7 for example) and an IgG antibody (see column 8 for example).

Shalaby et al. teaches a method of using anti-TNF-alpha antibodies to prevent graft-verses-host disease (GVHD) in mice.

Shalaby et al. suggests that antibodies to TNF-alpha may be a useful adjuvant for the treatment of GVHD in humans (discussion last paragraph in particular).

Brennan et al. teach a method of using anti-TNF-alpha antibodies to prevent IL-1 production in mononuclear cells from patients with rheumatoid arthritis and suggest that injection of anti-TNF-alpha antibodies locally into a rheumatoid joint may be a useful therapy in severe rheumatoid arthritis (p.244, introduction and p. 246 second column in particular).

Piguet et al. (1987) teach a method of preventing/treating GVHD in mice using anti-TNFα antibodies. Piguet et al. teach that the treatment almost entirely prevented the cutaneous and intestinal lesions of the acute-phase of GVHD, and markedly reduced overall mortality (see abstract for example).

Piguet et al. (1989) teach a method of treating pneumopathy and fibrosis using anti-TNFα antibodies. Piguet et al. teaches that bleomycin-induced pneumophathy and fibrosis in mice was effectively treated with anti-TNFα antibodies preventing alveolar damage, growth of fibroblasts, and collagen deposition (see page 661 for example).

Grau et al. teach a method of preventing/treating cerebral malaria disease using anti-TNFα antibodies.

Shalaby et al., Brennan et al., Piguet et al. (1987 and 1989), and Grau et al. all teach antibodies that block the

biological activity of TNFα but do not teach the specifically teach the claimed epitopes.

The Moller et al. references teach a method of using the monoclonal antibody M195 which appears to be the same as the antibody of the present invention. M195 is functionally similar to the A2 antibody as characterized in the specification, in exhibiting high affinity binding to TNFα, neutralizing TNFα but not TNF-beta (see p. 164 Table 2, Cytokine) binding to human and chimpanzee TNF but not TNF from baboon, rhesus monkey or cynomolgus monkey (e.g. cytokine, p164 col. 1). In view of those similarities, the A2 and M195 antibodies appear to have the same or similar epitope binding specificities and M195 is expected to have the properties recited in the instant claims. Moller et al. does not teach chimeric anti-TNFα antibodies.

Rathjen et al. (WO 9102078) teach high affinity TNF-specific antibodies which bind to neutralizing epitopes. Certain of these antibodies bind to epitopes located within synthetic peptides corresponding to TNFα, which contain an epitope recognized by the A2 antibody. According to the teaching of the specification the A2 antibody binds to synthetic peptides comprising residues 87-108 and 59-80. According to the teaching on page 33 of the reference, Mab 1 binds to a peptide consisting of residues 58-65, Mab 11 binds to a peptide consisting of residues 49-98, Mab 42 binds to a peptide consisting of residues 49-96, Mab 54 binds to

a peptide consisting of residues 56-79, etc. Results of competitive binding assays using the referenced antibodies are shown in Fig 9. The antibodies are shown to inhibit biological activities of TNFα according to the teaching in Table 2 , page 22. At least some of the referenced antibodies would be expected to competitively inhibit binding of Mab A2 of the instant invention to TNFα and to have the ID50 values recited in the claims. Rathjen et al. does not teach chimeric anti-TNFα antibodies.

Morrison teaches that chimeric antibodies were considered to be superior to rodent antibodies for use in in vivo therapies (Hospital Practice, page 66) and teach that methods for producing chimeric antibodies were well established in the art at the time the invention was made (Science, page 1207 for example).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to chimerize the antibodies of Moller et al. (U.S. Patent 5,231,024 or Cytokine, 1990) or Rathjen et al. using the method Morrison et al. (Science, 1985 or Hospital Practice, 1989) for the treatment GVHD as taught by Shalaby et al. or rheumatoid arthritis as taught by Brennan et al. or GVHD as taught by Piguet et al. (1987) or pneumopathy and fibrosis as taught by Piguet et al. (1989). One of ordinary skill in the art at the time the invention was made would have been motivated to chimerize the

antibodies of Moller et al. to prevent human anti-mouse antibody antibodies (HAMA).

It is known in the art that murine antibodies have characteristics which may severely limit their use in human therapy. As foreign proteins, murine antibodies may elicit immune reactions that reduce or destroy their therapeutic efficacy and/or evoke allergic or hypersensitivity reactions in patients. The probable need for re-administration of such therapeutic modalities in one of the above disorders increases these risks. Further tissue injury could occur by virtue of antigen-antibody deposition.

The claimed antibodies do not appear to differ in any unexpected or unobvious manner from those that one of ordinary skill in the art would have expected to obtain in view of the teachings of Moller or Rathjen et al. in combination with Morrison. Applicant has presented no evidence which is supportive of a conclusion that the claimed chimeric antibodies differ in any unexpected or unobvious manner from those that would have been suggested by the combined teachings of Moller or Rathjen et al. in combination with Morrison. It is noted that the TNFα protein is small and would be expected to have a rather limited number of epitopes. Moreover, the number of epitopes involved in receptor binding is even further reduced. Therefore, is far more likely than not that the antibodies of Moller or

Rathjen et al. meet the claim limitations in binding the same epitopes and competing with the A2 antibody.

Response to Applicant's Remarks

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

The Applicant argues:

1. That the references themselves do not suggest the combination of the A2 epitope or any particular isotype. In regards to the A2 epitope, M195 is functionally similar to the A2 antibody as characterized in the specification, in exhibiting high affinity binding to TNFα, neutralizing TNFα but not TNF-beta (see p. 164 Table 2, Cytokine) binding to human and chimpanzee TNF but not TNF from baboon, rhesus monkey or cynomolgus monkey (e.g. cytokine, p164 col. 1). In view of those similarities, the A2 and M195 antibodies appear to have the same or similar epitope binding specificities and M195 is expected to have the properties recited in the instant claims. Moreover, there is no reason to expect that routine antibodies to TNFα would not bind the A2 epitope. As for the isotype, the IgG1 isotype is a mere alternative to the IgG2,3 or 4 isotypes. The art recognized at the time the invention was made that the different isotypes had some functional differences (Morrison, Hospital Practice, 1989, page 77). One of ordinary skill in the art would have conducted

a simple screening procedure or referred to the general wealth of knowledge in the art at the time the invention was made to select an isotype with the desired activities. Importantly, the art recognized that the constant regions of the isotypes were interchangeable when constructing chimeric antibodies.

2. That the references only teach in vitro and in vivo animal models, and do not teach how to administer the antibodies in humans. The Applicant is reminded that their only needs to be a reasonable expectation of success. The purpose of in vitro and animal experimentation is to provide one of ordinary skill in the art with a correlation or reasonable expectation of what would occur in a human. Although some models to do not correlate as well as others, they generally do provide a reasonable correlation. For example, in regards to Brennan et al. (1989), Elliott et al. 1995 (page 142) states that the data of Brennan et al. "suggest that although there might be redundancy of cytokines within the synovial compartment in RA, there is also hierarchy, with TNFα in a controlling position." Maini et al. (1995) state that their "hypothesis that TNFα is a potential target for therapeutic intervention in RA was derived from experiments performed in vitro on RA synovial tissue....Using a polyclonal anti-TNF antibody to block TNFα activity in the RA synovial cell cultures, we observed that this also resulted in the inhibition

of IL-1 production (Brennan et al. 1989). The result suggested the presence the presence of a 'cytokine cascade' within the synovium, with the prediction that blockade of a pivotal cytokine in this network would subsequently lead to blockade of other [pro-inflammatory] cytokines 'downstream'." The Applicant is reminded that the claims are drawn to a method of treatment not a cure. Even if other cytokines were involved, a substantial effect would have been expected because the biological activity of the pro-inflammatory cytokines IL-1 and TNFα are both reduced with anti-TNFα antibodies. It is clear, therefore, that there would have been a reasonable expectation of success based on Brennan et al. (1989).

As for Shalaby et al. (1989), Applicant has not provided any objective evidence why their results would have reasonably expected the results to correlate in humans. Animal models incorporate the complex environment and generally correlate well with humans. One of ordinary skill in the art would certainly have reasonably expected success in humans in view of Shalaby et al. The argument that because the reference do not teach administration to humans the rejection is improper is not persuasive. Antibodies had been routinely administered to humans for more than a decade prior to time the invention was made. Chimeric antibodies were being used for several years as well. The Applicant has provided no objective evidence that the

treatment regimen of the claimed invention was not obvious in view of the general knowledge of antibody administration at the time the invention was made. It is noted that the Applicant is given priority to the earliest case, which teaches only the most rudimentary administration of antibodies in humans because that is all that was necessary. No unexpected treatment regimen was necessary for the treatment to be effective.

3. That one could not have predicted the affect of the antibodies of Moller et al. and Rathjen et al. in vivo from in vitro experimentation. Determining the pharmacokinetics of an antibody was routine in the art at the time the invention was made. Moreover, demonstration of specific binding and ability to neutralize activity is a good indication of the affects that antibody would have in vivo. One of ordinary skill in the art would have reasonably expected the in vitro results to correlate with those in vivo. The Applicant has not provided objective evidence to demonstrate otherwise.

4. That the references do not provide any motivation to chimerize the anti-TNF antibodies. The motivation to chimerize antibodies at the time the invention was self-evident when the antibody was going to be used in vivo and was taught by Morrison. It is true that HAMA might occur in response to a chimeric

antibody. However, one would have reasonably expected that the immune response to a chimeric antibody would be reduced when compared to murine antibody. Moreover, humanization using CDR grafting of antibodies often leads to reduced binding and sometimes eliminates binding. Chimerization would have been more predictable and more than likely faster than humanization.

5. That they have demonstrated unexpected results. Applicant argues that Kingsley et al. and Feldmann cast doubt on the ability of anti-TNFα antibodies to effectively treat RA. It is pointed out that both references appears to be unaware of Brennan et al. or Shalaby et al. in that neither cite Brennan et al. or Shalaby et al. One of ordinary skill in the art would have reasonably expected the results obtained based on the teachings of Brennan et al. and Shalaby et al.

4. Claims 119-122 are allowable.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John M. Lucas whose telephone number is (703) 305-6838. The examiner can normally be reached on M-T from 8:00am to 6:00pm EST.

6. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 305-3014 or 305-7939.

7. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

John M. Lucas, PhD

13 January 1998

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800